

Nephritic Syndrome

Introduction

In order to answer a question about glomerular diseases, you need three things: the clinical history, labs to tell you nephritic or nephrotic, and the renal biopsy. If you have two, you should be able to deduce the third. And that's how the test will approach this. You must be able to spot nephritic syndrome, recognize classic associations of each disease, and then know the biopsy results. "Biopsy results" means the appearance on light microscopy, electron microscopy, and immunofluorescent pattern. This paragraph should feel familiar—it is identical to the one that started Injury #4: *Nephrotic Syndrome*.

In this lesson, we are covering the nephritic diseases. **Nephritic syndrome** is a product of entire cells exiting the glomerular capillary lumen. This greatly compromises GFR, resulting in renal failure, as indicated by an elevated BUN (azotemia) and **elevated creatinine**. It is a syndrome of the glomerulus, so the tubules (at first) continue to function as they ought to. A compromised GFR is sensed by the macula densa, which triggers JG cells to release renin, leading to both angiotensin 2 and aldosterone expression. Angiotensin 2 "tenses the angios," inducing **hypertension**. Aldosterone increases reabsorption of sodium from the collecting duct—whatever is filtered is reabsorbed. This contributes to hypertension and periorbital edema.

Nephritic syndromes result in **hypercellularity**, either from endocapillary proliferation (mesangial cells and endothelial cells), from epithelial proliferation, or from influx of cells of innate immunity. Nephritis, the -itis of nephrons, means inflammation. Inflammation means white cells are exiting the capillary. Because white blood cells are larger than red blood cells, if white blood cells are exiting the capillary, red blood cells can too. Red blood cells "getting out" means **dysmorphic red blood cells** in the urine. And, if there are many red blood cells getting out of the capillary into Bowman's space (that's called bleeding into the glomerulus), they may get packed together, and form **red blood cell casts**. The only way to get dysmorphic red blood cells or red blood cell casts in the urine is glomerulonephritis.

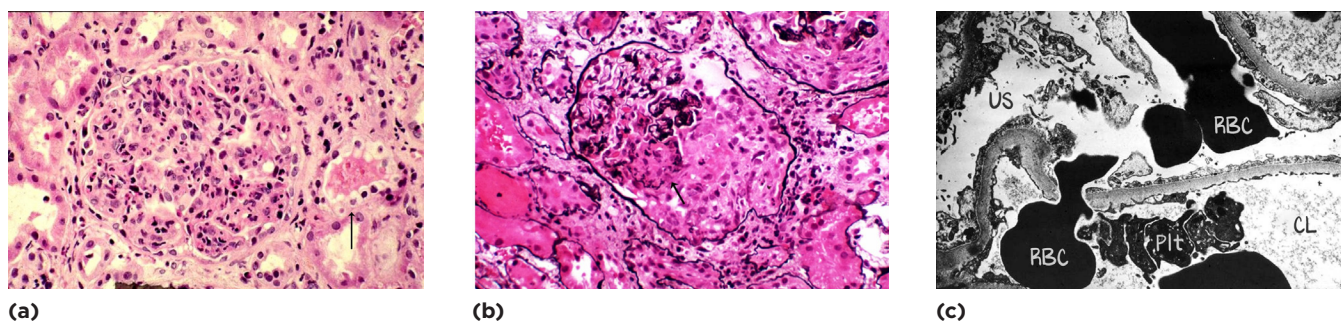


Figure 5.1: Nephritic Syndrome

(a) Diffuse Proliferative Glomerulonephritis, High power LM of a hypercellular glomerulus; numerous capillaries contain inflammatory cells, mostly neutrophils. Notice the red blood cells in a distal tubule, to the right of the glomerulus (b) Focal proliferative and necrotizing glomerulonephritis. Both glomeruli have cellular crescents, and the central glomerulus has segmental proliferation and a break in the GBM (arrow). Jones methenamine silver. (c) This electron micrograph shows a red blood cell caught in the act of traversing the glomerular capillary wall through a breach in its basement membrane. Several aggregated platelets (Plt) are at the ready to "plug" the hole. A few red cells have already traveled downstream and are found in the urinary space (US). Those RBCs that reach the proton-secreting segments of the distal tubules in the company of protein-containing filtrate will be incorporated into a RBC cast due to the denaturing action of the acid environment.

Acute Proliferative Glomerulonephritis/Poststreptococcal Glomerulonephritis

Acute proliferative glomerulonephritis (APG) can be caused by more than just strep infections. But because streptococcal-induced APG is the prototypical form of APG, we want you learning APG as the same thing as poststreptococcal glomerulonephritis (PSGN). Technically, APG describes a glomerulus with acute inflammatory cells (neutrophils and macrophages), and is a histologic diagnosis. We are going to treat the histologic appearance APG and the diagnosis PSGN as synonymous.

PSGN is a type III hypersensitivity reaction, caused by **immune-complex deposition**. The antigen-antibody complexes are preformed, circulating in plasma. This immune-complex deposition is related to the filtration barrier, and so may sound familiar to the pathogenesis of some nephrotic diseases. However, these immune-complex depositions do not cause effacement of podocytes. This is because the accumulation of deposits is sparse and temporary, and will pass spontaneously. Instead, these immune-complex depositions **activate complement**. Activation of complement **consumes complement** in the generation of **C5a** (the chemoattractant complement). This informs the cells of the innate immune system—neutrophils and macrophages—to exit the capillary and enter tissue. Since there are these immune deposits in every glomerulus (the antibody-antigen complexes go wherever blood goes), the innate immune system starts fighting the “invaders” stuck in filtration slits in every glomerulus. In their fight to destroy the tagged antigen, they end up taking healthy glomerulus with it.

PSGN and rheumatic heart disease are both possible sequelae of strep pharyngitis. Rheumatic heart disease is caused by antigenic mimicry. PSGN is caused by immune-complex deposition. The **M protein** on the surface of certain group A *Strep. pyogenes* strains is the causative agent. Antibodies form to the M protein. In assessing a patient who might have PSGN, we draw levels of antibodies against streptolysin-O to make the diagnosis of a recent strep infection. However, the antigen-antibody deposition is caused by antibodies made to the M protein.

One to four weeks following an untreated strep pharyngitis or strep impetigo, the patient may develop nephritic syndrome. PSGN is far more common in children (who recover most of the time) than in adults (who, if they get PSGN, are likely to progress to renal failure). If a biopsy is done, it will show **enlarged hypercellular glomeruli** on light microscopy. The epithelium of Bowman's space is normal, the glomerular tuft expanded into the available space. Cytokines released during the process of inflammation may also induce mesangial cells to proliferate, further hypercellularizing the glomerular tuft. This is an immune deposition disease, so will demonstrate **granular pattern** on immunofluorescence, with positivity for **IgM, IgG, and complement**. Complement levels in the blood will be low. On electron microscopy, there are large **subepithelial deposits** called “humps” and smaller subendothelial deposits. The hypothesis is that the deposits work their way through the basement membrane and coalesce on the subepithelial side. These do cause podocyte effacement wherever they coalesce, but do not cause nephrotic syndrome because the vast majority of pedicles are not effaced. The deposits are too few in number, with great stretches of normal podocyte foot processes between them. Instead, they coalesce until they are released into the urine, where they are passed without further problem.

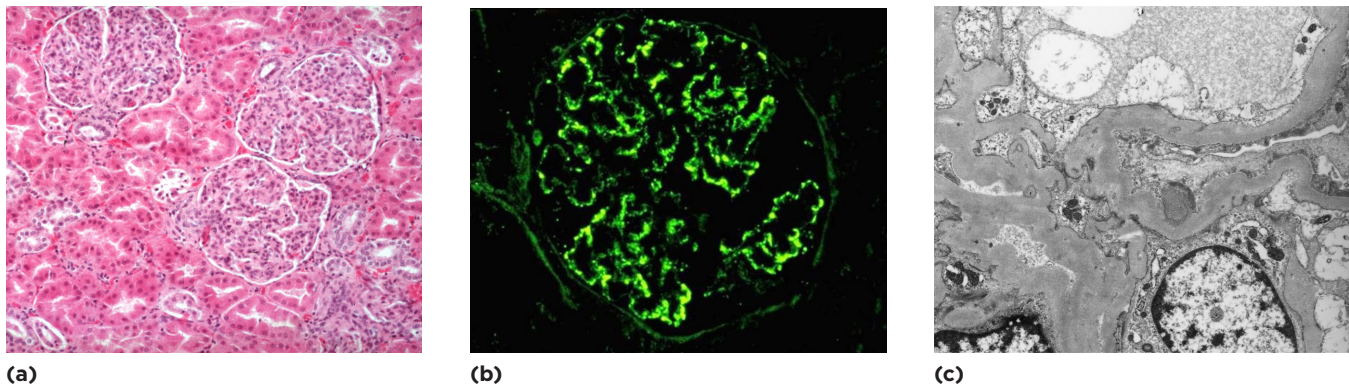


Figure 5.2: Acute Proliferative Glomerulonephritis

(a) Light microscopy reveals several glomeruli that are hypercellular, expanding the glomerular tuft. The increased number of purple dots (nuclei) are indicative of inflammatory cells. (b) immunoglobulin deposition in a case of post-streptococcal GN with nephrotic range proteinuria during the recovery phase. This form of post-streptococcal glomerulonephritis can be confused with membranous GN. (c) Electron microscopy demonstrates only a single subepithelial deposit (center, dark grey) and several miniscule subendothelial deposits forming.

And that is why the treatment for this involves **supportive care only**. The deposits will take care of themselves. As the infection is treated, the antigen eliminated, the antigen-antibody complexes no longer form. Since the deposits coalesce and pass into the urine, as time passes, there are fewer and fewer deposits, less and less inflammation, and the glomerulus returns to normal. Children generally have asymptomatic resolution without long-term consequences to renal function. In adults, there is a risk of developing rapidly progressive (crescentic) glomerulonephritis, discussed next.

Rapidly Progressive (Crescentic) Glomerulonephritis

Like APG, rapidly progressive glomerulonephritis (RPGN, formerly called crescentic) represents a histologic symptom and not a diagnosis in and of itself. All causes of RPGN are immune-mediated, but use varying immunologic mechanisms. These diseases have been lumped together because they all show the same light microscopy appearance—the presence of crescents. **Crescents** represent proliferation of the **parietal layer** of Bowman's capsule. Within the crescents are **macrophages** and **fibrin**. Crescents grow from the outer layer of Bowman's space inward, eventually impinging on the glomerular tuft. As the glomerular tuft gets smushed, the **basement membrane wrinkles** and sometimes **breaks**, as can be seen on electron microscopy.

The finding of crescents is not a good sign, and RPGN can result in end-stage renal failure in weeks to months. The clinical course an individual patient will take depends on the underlying etiology that generated the immune response in the first place. This is very unlike the progression of renal failure in general, as discussed in Injury# 3: *Glomerular Filtration*, where there was a steady progression toward renal failure after compromise of 30%–50% of the GFR.

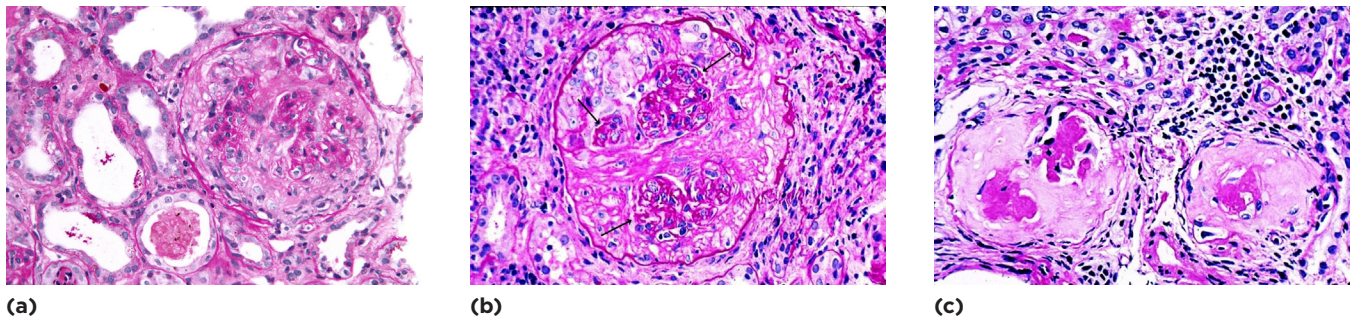


Figure 5.3: Rapidly Progressive Glomerulonephritis

(a) Glomerulus revealing prominent segmental hypercellularity. Glomeruli are involved with some degree of “extracapillary proliferation” (crescent formation) outside the tuft but inside Bowman’s capsule. (b) A fibro-cellular crescent. Notice the collapsed and fragmented capillary tuft (arrows). (c) Chronic stage, with fibrotic crescents that have obliterated and fragmented the glomerular tuft. The remnants of the original tufts can be recognized as strongly positive PAS material within the pale-staining scar tissue that represents the acellular and now completely organized crescent.

There are three subtypes classified by immunofluorescence pattern. All RPGNs show crescents on light microscopy. All RPGNs show basement membrane fragmentation on electron microscopy. Some show deposits on electron microscopy. The immunofluorescence is how medical science has chosen to categorize the subtypes of RPGN—type 1, linear; type 2, granular; type 3, pauci-immune.

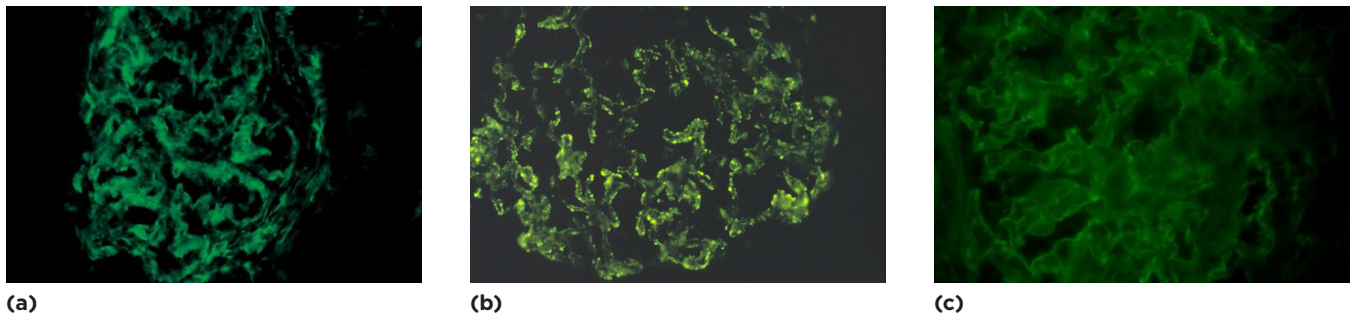


Figure 5.4: RPGN Immunofluorescence Subtypes

(a) Linear immunofluorescence found on RPGN histology taken from a patient with Goodpasture’s syndrome. B) Sample from a patient with lupus nephritis demonstrating a granular pattern. (c) The nebulous, pauci-immune pattern seen in Wegner’s.

Type 1 RPGN demonstrates a **linear immunofluorescence pattern**, indicating that there are antibodies against glomerular membrane proteins and not deposition of immune complexes. This is the immunofluorescence pattern seen in **Goodpasture’s disease**, caused by antibodies to **intrinsic antigens distributed throughout the basement membrane**. The antibodies are named antiglomerular basement membrane antibodies (anti-GBM). Because these antigens are part of the basement membrane, they are fixed antigens. Fixed antigens cannot coalesce to form deposition. Anti-GBM antibodies affect both the **glomerulus** (causing **hematuria**) and the basement membrane of **alveoli** (causing **hemoptysis**). The presentation of hemoptysis and hematuria should make you think immediately of Goodpasture’s disease. However, as discussed below, granulomatosis with polyangiitis, the vasculitis formerly known as Wegener’s, can also present with hemoptysis and hematuria. The difference is in the sinus symptoms and the immunofluorescent pattern.

Type 2 RPGN demonstrates a **granular immunofluorescence pattern**, indicating an immune-complex deposition. Electron microscopy will reveal **subendothelial deposits**, indicating preformed antigen-antibody complexes. In patients with lupus who develop renal failure (**lupus nephritis**), type 2 RPGN is the most common mechanism. Be cautious—lupus is caused by antibodies to a variety of antigens,

and either nephritic or nephrotic immune-deposition diseases can be seen in lupus. You should associate type 2 RPGN and lupus nephritis. But the presence of a lupus diagnosis in a vignette should not cause you to assume that the stem is about type 2 RPGN. In addition, any other disease with a pathogenesis of preformed immune-complex deposition could result in type 2 RPGN. This includes the PSGN discussed above. In patients who do not self-resolve, PSGN usually progress through type 2 RPGN toward end-stage renal disease. We've got lupus nephritis and progressive PSGN as causes of type 2 RPGN. The last disease you should be aware of its Henoch-Schönlein purpura (discussed in Rheumatology), which can also result in type 2 RPGN.

Be careful not to confuse RPGN and MPGN. The preformed immune-complex deposition that results in **renal failure**, a granular immunofluorescence, **crests** on light microscopy, and subendothelial deposits on electron microscopy, is type 2 RPGN. The preformed immune-complex deposition that results in **proteinuria** only, with a granular immunofluorescence, **basement membrane thickening/tram-tracking** on light microscopy, and subendothelial deposits on electron microscopy, is MPGN (a nephrotic syndrome).

Type 3 RPGN demonstrates a **pauci-immune pattern**. The only time you will ever hear the words pauci-immune is in relation to RPGN. All it means is that there is some, but not a whole lot, of immunofluorescence. You see crescents on light microscopy and perform immunofluorescence, expecting to decide between linear and granular, but then get a diffuse, weak signal instead. In 90% of cases, RPGN with pauci-immune pattern is **idiopathic** and involves only the kidney, suggesting that type 3 RPGN may be a previously unnamed vasculitis that is localized to the glomerular capillaries. In 10% of cases, type 3 RPGN is associated with one of three named vasculitis diseases that are typically associated with pauci-immune pattern RPGN—Wegener's, Churg-Strauss, and microscopic polyangiitis.

Type 3 RPGN is caused by a vasculitis. Ninety percent of the time, the vasculitis is isolated to the kidney. Ten percent of the time, the vasculitis is connected to a vasculitis disease that affects vessels outside the kidney. Each of these vasculitis diseases is associated with **ANCA** (antineutrophil cytoplasmic antibodies).

Wegener's, now called **granulomatosis with polyangiitis**, is associated with **cANCA**. It presents with hematuria and hemoptysis (just like Goodpasture's), but also presents with **sinus symptoms** (nasopharynx involvement). Any involvement of the face or sinuses should lead you away from Goodpasture's. Of course, a biopsy with immunofluorescence would show you which diagnosis you have. Churg-Strauss is vasculitis of small and medium arteries associated with **asthma and eosinophilia** with a **pANCA**. The other pANCA vasculitis disease is microscopic polyangiitis, and is the "diagnosis left over" (pauci-immune, pANCA, and not-Churg-Strauss).

IDIOPATHIC	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS	MICROSCOPIC POLYANGIITIS
cANCA	cANCA	pANCA	pANCA
Isolated renal failure, hematuria	Hemoptysis, hematuria, and sinuses	Asthma, eosinophilia	Not the other ones
"cANCA only"	"cANCA plus"	"pANCA plus"	"pANCA only"

Table 5.1

IgA Nephropathy/Berger's Disease

IgA nephropathy is the **most common glomerulonephritis** in the world. It is also a **deposition disease** (type III hypersensitivity). When faced with a mucosal infection (upper respiratory tract infection, for example), mucosal antibodies are generated. Mucosal antibodies are **IgA**. When that mucosal infection induces proliferation of B cells and secretion of extra IgA to fight that infection, IgA is released into the bloodstream and circulates everywhere. Sometimes, as in IgA nephropathy, **IgA antibodies deposit** in the **mesangium**. IgA nephropathy is the only nephritic or nephrotic syndrome that involves the mesangium. Nephritis symptoms tend to occur near to the time of the mucosal infection (days), as opposed to the PSGN being weeks out from a pharyngitis (which is also a mucosal infection).

The **mesangium proliferates** in response to the deposition, resulting in endocapillary proliferation, not infiltration by crescents. **Light microscopy** will show a mesangial proliferation, hypercellularity inducing swelling of the glomerular tuft. There is no basement membrane thickening or release of proteinaceous material. On **immunofluorescence**, because it is an immune deposition disease, you can expect to see a **granular pattern**. What you've seen over and over up to this point is the net-like immunofluorescence induced by deposition at the glomerular basement membrane. There is deposition in this disease. There is not deposition at the GBM, but rather in the mesangium. Instead of the net-like appearance staining the capillary lining, everywhere that didn't light up in the other diseases lights up in this disease. **Electron microscopy** can be used to see deposits in the mesangium, but there is often no need for electron microscopy.

Infiltration of IgA and proliferation of mesangial cells leads to hematuria. Patients will present with **repeated episodic hematuria**, always following some mucosal infection. Because the infection resolves, IgA production reduces, and the immunoglobulins clear from the mesangium. Renal function returns to business as usual. With repeated attacks, fewer glomeruli remain. Fifty percent will progress to end-stage renal disease.

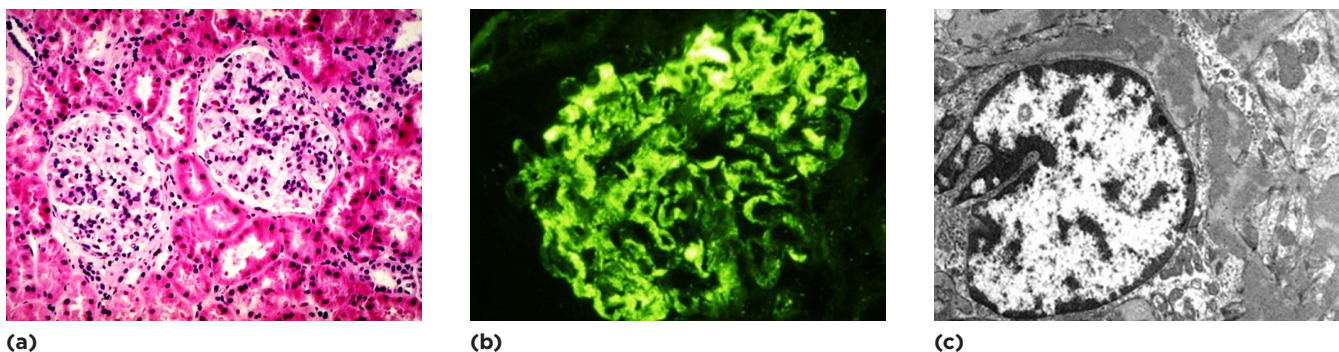


Figure 5.5: IgA Nephropathy

(a) Light microscopy shows two glomeruli show a well-preserved structure with only moderate expansion of the mesangial matrix and mild focal mesangial hypercellularity (b) Immunofluorescence microscopy with anti-IgA; detail of a glomerulus with mesangial deposits only. Notice the peripheral capillary walls are only outlined by the background staining; no deposits are seen. (c) Mesangial proliferation on EM.

Alport Syndrome

Alport's is **not autoimmune**. It is caused by over 500 known mutations of any of the genes that code for collagen. Because the genes for collagen are on chromosomes 2, 13, and the X chromosome, the inheritance pattern can be autosomal or X-linked. In the most severe form of the disease, the one you will see on your licensing exam, it is an **X-linked dominant disease** that demonstrates large deletions of the $\alpha 5$ chain gene. In girls, heterozygous patients will present only with hematuria. In **boys**, who have only one X chromosome, patients will present with **nephritic syndrome, hearing loss, and blindness** (ears and eyes also rely on collagen type IV). This clinical scenario is sufficient for the diagnosis, especially if there is overt nephritic syndrome. No other nephritic disease causes blindness or hearing loss. The worse the mutation, the worse the symptoms will be. Males with the X-linked dominant inheritance go into end-stage renal disease at an early age. The disease itself is rare.

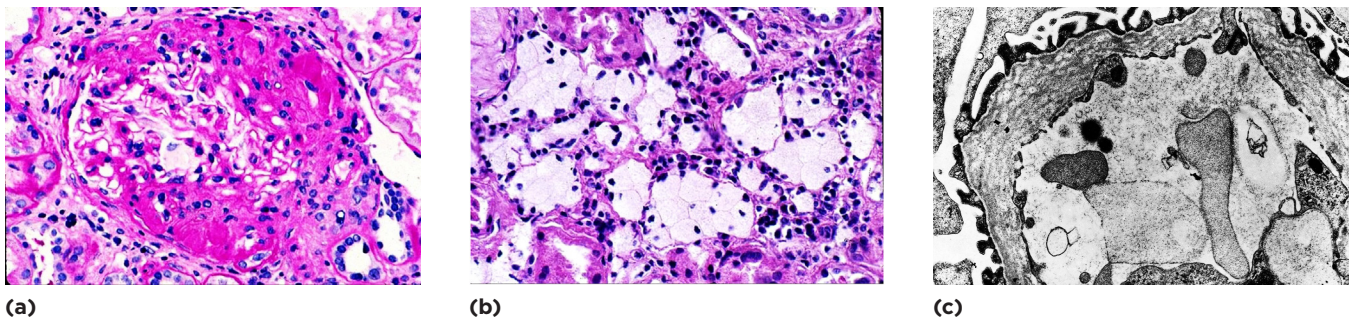


Figure 5.6: Classical Alport's Syndrome Due to X-linked Hereditary Nephritis

(a) There is focal and segmental sclerosis of this glomerulus in this 22-year-old male patient with significant proteinuria and moderate renal insufficiency. (PASH) (b) Interstitial foam cells are often a clue to the diagnosis in patients without hyperlipidemia (c) . There is prominent lamination and fraying of the GBM. Notice the extreme fragmentation of the lamina densa, resulting in a characteristic "basket weave" pattern.

Light microscopy is nonspecific. There is no immunoglobulin or complement involved, so immunofluorescence is useless. Instead, what you should look for is **alternating thickening and thinning** of the basement membrane on electron microscopy (what others call a "basket weave" appearance). With a defective gene as the cause, there is **no treatment**.

DISEASE	ASSOCIATIONS
Poststreptococcal glomerulonephritis (PSGN) aka Acute proliferative glomerulonephritis (APGN)	Child 6-10 years of age 2-4 weeks after strep infection develops nephritic syndrome 2/2 to M protein on strep Preformed antigen-antibody complex deposits appear on subepithelial side, coalesces on subepithelial side, then vanish, supportive care only Light: Endocapillary proliferation EM: Subepithelial humps IF: Granular IgM, IgG, C3
Rapidly progressive glomerulonephritis	All RPGN show crescents, epithelial proliferation and invasion by leukocytes Crescents are made of fibrin and macrophages Crescents smooch tuft, wrinkle and fracture basement membrane Light: Crescents EM: Wrinkled BM, fractured BM IF: Defines types of RPGN
RPGN 1 Goodpasture's	IF: Linear RPGN Anti-GBM antibodies target collagen 4 of shared basement membranes Targets alveoli and glomerulus, presents as hemoptysis and hematuria
RPGN 2 Lupus nephritis	IF: Granular RPGN Antigen-antibody complexes cause subendothelial deposits May also be a progression from APGN (which also has deposits)
RPGN 3 Pauci-immune, aka vasculitis	IF: Pauci-immune Most common is isolated renal vasculitis, associated with cANCA Wegener's (granulomatosis with polyangiitis) is "cANCA plus" <ul style="list-style-type: none"> • Hemoptysis and hematuria with sinus involvement, cANCA positive Churg-Strauss is "pANCA asthma" <ul style="list-style-type: none"> • Asthma, eosinophilia, and nephritis Microscopic polyangiitis is "pANCA-not-Churg-Strauss"
IgA nephropathy	IgA deposits in mesangium During or 2 days after a mucosal infection, nephritic syndrome (compare PSGN) Light: Endocapillary mesangial proliferation EM: not needed IF: Granular IgA within mesangium
Alport syndrome	X-linked (boys) defect of type IV collagen Non-autoimmune Boys with hearing loss, vision problems, and nephritic syndrome EM: Alternating thickening and thinning of basement membrane

Table 5.2: Nephritic Syndromes